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ORIGINAL RESEARCH

Clinicopathological and Genomic Analysis of *SMARCA4*-Deficient Non-Small Cell Lung Cancer: A Retrospective Cohort Study

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Background: *SMARCA4*-deficient non-small cell lung cancer (*SMARCA4*-dNSCLC) is a rare, aggressive subtype with limited treatment options. This study analyzed clinical, pathological, molecular, and prognostic features to improve recognition and identify survival determinants.

Methods: This retrospective cohort study included 47 patients with pathologically confirmed *SMARCA4*-dNSCLC diagnosed at Anhui Chest Hospital between July 2022 and January 2024. *SMARCA4* deficiency was defined as loss of BRG1 expression by immunohistochemistry. Clinical data, imaging findings, histopathology, molecular profiles, treatment modalities, and follow-up outcomes were reviewed. Overall survival (OS) was analyzed using Kaplan-Meier curves and Cox proportional hazards regression models to determine independent prognostic factors.

Results: The cohort was predominantly older male smokers (median age 66; 87% male) with advanced disease (47% with distant metastasis at diagnosis). Imaging typically showed large, necrotic masses with ill-defined borders. Adenocarcinoma was the most common subtype (60%). Immunohistochemistry revealed BRG1 loss (91%), frequent *TTF-1* negativity, and high Ki-67 expression. Common genetic alterations included *TP53*, *KRAS*, and *STK11* mutations, while *EGFR* mutations were rare. Median overall survival was not reached in the treated group (median follow-up: 12.3 months; IQR: 8.5–15.1 months), compared with 3 months in the untreated group (median follow-up: 4.2 months; IQR: 2.8–5.6 months). Advanced TNM stage, distant metastasis, and absence of treatment were independent adverse prognostic factors ($p<0.05$).

Conclusion: *SMARCA4*-dNSCLC represents a distinct clinicopathologic entity with poor outcomes. Given the aggressive nature and poor prognosis of untreated *SMARCA4*-dNSCLC, timely diagnosis and multimodal treatment are essential to improving survival. Further prospective studies are needed to optimize management strategies.

Keywords: *SMARCA4*-deficient lung cancer, BRG1 loss, immunohistochemistry, prognosis, treatment outcome, molecular profiling

Introduction

SMARCA4-dNSCLC is an emerging, biologically distinct, and highly aggressive subtype of lung cancer characterized by the inactivation of the *SMARCA4* gene,[1–3] which encodes the BRG1 protein, a core catalytic subunit of the SWI/SNF chromatin remodeling complex.[4–6] This subtype is increasingly recognized for its unique clinical and pathological features, most notably its predilection for older male patients with a history of heavy smoking.[7]

The loss of BRG1 protein expression, as determined by immunohistochemistry, is a hallmark diagnostic feature of *SMARCA4*-dNSCLC.[8,9] Histologically, these tumors frequently display poorly differentiated or undifferentiated morphology, often with rhabdoid or solid features, making diagnosis challenging, especially in small biopsy specimens.[10–12] Moreover, these tumors typically lack common targetable driver mutations such as *EGFR* and *ALK*, limiting therapeutic options. As a result, conventional treatments including surgery, chemotherapy, and radiotherapy have shown limited efficacy in this population. Clinical outcomes remain dismal, with reported median OS as short as six months in many

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studies. *SMARCA4* encodes the BRG1 protein, a core catalytic subunit of the SWI/SNF chromatin remodeling complex that regulates gene transcription through ATP-dependent chromatin accessibility. Loss of BRG1 disrupts the regulation of key pathways involved in cell cycle control, DNA repair, and differentiation, driving malignant transformation and enhancing tumor aggressiveness.[13] Additionally, *SMARCA4* deficiency is associated with increased genomic instability and altered tumor immune microenvironment, which may influence responses to chemotherapy and immunotherapy.[14] These biological features further underscore the uniqueness of *SMARCA4*-dNSCLC and the need for targeted research.

Notably, *SMARCA4*-deficient NSCLC is closely related to *SMARCA4*-deficient undifferentiated tumor (*SMARCA4*-UT), both characterized by loss of BRG1 expression. However, *SMARCA4*-dNSCLC retains epithelial differentiation markers (eg, cytokeratin positivity) and NSCLC histologic features (eg, adenocarcinoma), while *SMARCA4*-UT lacks lineage-specific markers and exhibits undifferentiated morphology.[15] Clinically, *SMARCA4*-UT is more aggressive with shorter median survival, whereas *SMARCA4*-dNSCLC may have relatively better responses to conventional NSCLC therapies, reflecting a spectrum of SWI/SNF-deficient thoracic malignancies.[16]

Due to its rarity (accounting for 1–3% of NSCLC cases), overlapping morphology with other aggressive subtypes, and lack of routine BRG1 immunohistochemical screening, *SMARCA4*-dNSCLC is frequently under-recognized in clinical practice.[17,18] Key knowledge gaps include: (1) unclear correlation between molecular alterations (eg, co-mutations in *TP53*, STK11) and treatment responses; (2) lack of standardized diagnostic algorithms for early detection; (3) limited real-world data on prognostic factors specific to this subtype; and (4) absence of targeted therapies for patients with no actionable driver mutations.[17,19] There is a paucity of large-scale data describing its clinical presentation, imaging and pathological characteristics, molecular profiles, and treatment responses in real-world settings. Consequently, the prognostic factors affecting survival outcomes in this subgroup remain poorly defined.

Given the rarity of *SMARCA4*-dNSCLC and unclear prognostic factors, we hypothesized that this subtype exhibits distinct clinicopathological/molecular features associated with survival, and that active multimodal treatment could improve outcomes. Therefore, this study aimed to comprehensively analyze the clinical characteristics, pathological features, imaging findings, molecular alterations, treatment strategies, and prognostic factors in a cohort of 47 patients diagnosed with *SMARCA4*-dNSCLC at our institution. By better characterizing this rare entity, we hope to enhance its clinical recognition and provide evidence to inform risk stratification and therapeutic decision-making.

Materials and Methods

Study Design and Patients

This was a retrospective cohort study approved by the Medical Ethics Committee of Anhui Chest Hospital (Ethics Approval No. KJ2024-059). A total of 47 patients diagnosed with *SMARCA4*-dNSCLC at Anhui Chest Hospital between July 2022 and January 2024 were included. *SMARCA4* deficiency was defined as complete loss of BRG1 protein expression confirmed by IHC. For the 4 patients with partial BRG1 expression (9%), further molecular testing (Sanger sequencing) confirmed *SMARCA4* gene mutations (frameshift or nonsense mutations) leading to functional inactivation, thus meeting the diagnostic criteria for *SMARCA4* deficiency. Inclusion criteria were: (1) pathological diagnosis of *SMARCA4*-dNSCLC, (2) availability of complete clinical data, imaging studies, and follow-up survival information. Patients with incomplete essential information (eg, lack of confirmatory IHC or missing follow-up) were excluded.

Data Collection

Clinical and pathological data were retrieved from medical records and pathology databases. Imaging reports were reviewed by two board-certified radiologists. Follow-up data were obtained through outpatient visits and/or telephone interviews. The following variables were collected.

Clinical data: Age, sex, smoking history (including pack-years when available), alcohol use, family history of lung cancer, history of tuberculosis, comorbidities (especially emphysema/COPD), presenting symptoms, and performance status (ECOG score if documented).

Pathological data: Diagnostic approach (surgical resection, bronchoscopy biopsy, or CT-guided percutaneous lung biopsy), histological subtype classified according to the 2021 WHO Classification of Thoracic Tumors, TNM staging based on the 8th edition of the AJCC staging system, and maximum tumor diameter.[20] IHC results included *BRG1* (*SMARCA4*), cytokeratin subtypes (*CK*, *CK7*), *TTF-1*, *Napsin A*, *p40*, *CDX-2*, *ALK*, *PD-L1* tumor proportion score (*TPS* categorized as <1%, 1–49%, ≥50%), and *Ki-67* labeling index (categorized as <10%, 10–50%, >50%). For patients undergoing surgery, pathological features such as vascular, pleural, bronchial, and neural invasion were recorded.

Imaging features: A total of 43 patients had complete chest CT data. The following features were evaluated: lesion location, morphology (mass, nodule, thick-walled cavity, subpleural consolidation), tumor margins (clear vs indistinct), size, internal components (eg, necrosis, calcification, air-fluid level), and enhancement characteristics (where available). Associated pulmonary conditions such as emphysema, chronic bronchitis, bullae, and interstitial lung disease were noted, as well as mediastinal or hilar lymphadenopathy, pleural or pericardial effusion, adrenal abnormalities, and metastatic spread. Vascular and airway involvement (eg, vessel encasement, bronchial truncation) were also assessed.

Molecular profiling: Next-generation sequencing (NGS) was performed in 24 patients. The NGS panels employed, though not identical across all patients (including both commercial and in-hospital platforms), consistently covered the key oncogenic driver genes analyzed in this study, including *EGFR*, *ALK*, *ROS1*, *KRAS*, *TP53*, *STK11*, *PIK3CA*, and *MET*. All testing was performed in certified clinical laboratories using standard procedures.

Treatment information: Treatment modalities included surgery, chemotherapy (platinum-based regimens such as cisplatin, carboplatin, or nedaplatin), immunotherapy (immune checkpoint inhibitors, agent details when available), targeted therapy (*EGFR*-TKI or *MET* inhibitors), radiotherapy (intent and site), and supportive care (Supportive care primarily included symptomatic management (eg, analgesia for pain relief), nutritional support, and adverse event monitoring for patients receiving anti-tumor therapy). For untreated patients, reasons such as economic burden, patient refusal, or advanced disease were documented.

Follow-up and survival: Follow-up was conducted via clinic visits or telephone interviews. The last follow-up date was July 28, 2024. OS was defined as the time from pathological diagnosis to death from any cause or to the last follow-up date for surviving patients.

Ethics Statement

This study was approved by the Ethics Committee of Anhui Provincial Chest Hospital (Approval Number: KJ2024-059). The study was conducted in accordance with the principles of the Declaration of Helsinki and relevant national laws and regulations.

Statistical Analysis

All statistical analyses were performed using SPSS version 17.0. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), and categorical variables as counts and percentages. Kaplan-Meier survival curves were generated to estimate OS, and differences between groups were compared using the Log rank test. Univariate Cox proportional hazards regression analysis was used to identify potential prognostic factors, including age, sex, smoking history, TNM stage, distant metastasis, treatment status, PD-L1 expression, Ki-67 index, and others. Variables with a P value < 0.10 in univariate analysis or considered clinically relevant were included in multivariate Cox regression models to identify independent predictors of survival. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. A two-sided $p< 0.05$ was considered statistically significant. Patients with missing key data (eg, IHC markers) were excluded from survival analysis. The proportional hazards assumption for Cox regression analysis was verified using Schoenfeld residual tests and log-log survival plots; no significant violations were observed (P > 0.05).

Results

Patient Cohort and Baseline Characteristics

This retrospective analysis of 47 *SMARCA4*-dNSCLC patients reveals distinctive demographic and clinical patterns. The cohort showed a marked male predominance (87.2%) with a median age of 66 years (range: 46–81 years). Smoking

history was prevalent (63.8%) and exclusively observed in male patients, as was alcohol consumption (31.9%), suggesting potential gender-specific risk factors. Tumor staging at diagnosis demonstrated the aggressive nature of this malignancy. While T-stage distribution varied (T1: 23.4%, T2: 21.3%, T3: 38.3%, T4: 17.0%), nearly half the patients (46.8%) presented with Stage IV disease. The mean tumor diameter was 48.42 ± 25.02 mm (range: 11–132 mm), with metastases commonly affecting multiple sites including lung, liver, brain, and bone. Anatomically, tumors favored the upper lobes, with the right upper lobe being the most frequent location (29.8%), followed by the left upper lobe (19.1%). Notably, 14.9% of cases exhibited multifocal or bilateral disease, indicating the cancer's invasive potential. Emphysema accompanied over half the cases (55.3%), reinforcing the smoking connection, while family history of lung cancer (6.4%) and tuberculosis history (10.6%) were less common. Most patients (63.8%) presented with respiratory complaints including chest tightness, dyspnea, cough, and hemoptysis. However, the asymptomatic discovery of cancer in 21.3% of patients during routine examinations highlights a significant challenge for early detection.

These findings characterize *SMARCA4*-dNSCLC as predominantly affecting older male smokers, often diagnosed at advanced stages, and exhibiting diverse clinical manifestations. This profile underscores the importance of thorough screening in high-risk populations and suggests potential pathways for targeted research and intervention. The detailed clinical and demographic characteristics of the cohort are summarized in Table 1.

Pathology and Immunohistochemical Features

The pathological analysis of the tumor samples provided critical insights into the histological characteristics of *SMARCA4*-dNSCLC in this cohort. The histological types of NSCLC observed were diverse, with adenocarcinoma being the most frequent (60%, 28/47 cases), including various subtypes such as poorly differentiated adenocarcinoma, infiltrative adenocarcinoma, and adenocarcinoma with other carcinoma components. Squamous cell carcinoma was identified in 3 cases (6%), while poorly differentiated carcinoma and undifferentiated carcinoma each accounted for 6 cases (13%) and 3 cases, respectively. Other less frequent histological types included large cell carcinoma, carcinoma, and mucinous epidermoid carcinoma. This histological heterogeneity highlights the morphological diversity of *SMARCA4*-dNSCLC, which can present diagnostic challenges, although the predominance of adenocarcinoma aligns with previous reports.

Immunohistochemical analysis revealed several key features. Cytokeratin (CK) expression was positive in the majority of cases (98%, 46/47), confirming the epithelial nature of these tumors. A subset of cases (64%, 30/47) showed *CK7* positivity. In contrast, *BRG-1* expression was completely negative in 43 patients (91%), and 4 patients (9%) showed partial expression with confirmed *SMARCA4* gene mutations (functional inactivation); all 47 patients met the diagnostic criteria for *SMARCA4* deficiency. Other markers, including *TTF-1* and *Napsin A*, showed variable expression, with *TTF-1* positive in 17 cases and negative in 29 cases, and *Napsin A* positive in 12 cases and negative in 21 cases. *P40* was positive in 7 cases and negative in 37 cases. The variable expression of *TTF-1* and *Napsin A* suggests that *SMARCA4*-dNSCLCs can exhibit a range of differentiation patterns, complicating accurate classification. *PD-L1* expression,

Table 1 General Characteristics of Patients Included in the Study

Characteristic	Statistics
Age (years)	Median: 66, Mean: 64.89 ± 9.94
Gender	Male: 41 (87.2%), Female: 6 (12.8%)
Smoking History	Present: 30 (63.8%)
Alcohol Consumption	Present: 15 (31.9%)
Clinical Symptoms	Respiratory symptoms: 30 (63.8%), Asymptomatic: 10 (21.3%), Other: 7 (14.9%)
TNM Staging	Stage I: 6 (12.8%), Stage II: 6 (12.8%), Stage III: 13 (27.7%), Stage IV: 22 (46.8%)
Tumor Diameter (mm)	Mean: 48.42 ± 25.02
Primary Tumor Location	Left upper lobe: 9, Left lower lobe: 7, Right upper lobe: 14, Right middle lobe: 4, Right lower lobe: 6, Bilateral multiple lesions: 2, Other: 3
Comorbidities	Emphysema: 26 (55.3%), Family history of lung cancer: 3 (6.4%), Tuberculosis history: 5 (10.6%)

evaluated in 39 cases, showed varying levels<1% in 17 cases, 1–49% in 20 cases, and ≥50% in 4 cases. This suggests that some *SMARCA4*-dNSCLCs may be potentially responsive to immunotherapy, although the varying *PD-L1* levels necessitate careful patient selection. The *Ki-67* proliferation index was high in most cases, with 64% (25/39) exhibiting>50% expression, indicative of a high proliferative rate and consistent with the aggressive nature of this cancer. These results are summarized in Table 2.

Microscopic examination of the tumor tissue revealed distinct morphological features. As shown in Figure 1A, the tumor cells displayed a loss of *BRG1* nuclear expression, a hallmark of *SMARCA4*-dNSCLC. These cells were also positive for *CK*, as shown in Figure 1B, confirming their epithelial origin. Histologically, the tumor exhibited coagulative necrosis with loosely cohesive, atypical cells arranged in sheets and nests. These cells were characterized by a high nuclear-cytoplasmic ratio, vesicular chromatin, prominent nucleoli, and eosinophilic cytoplasm, demonstrating significant cellular atypia (Figure 1C and D). These features are indicative of a highly malignant tumor with aggressive growth potential.

Characteristic Imaging Features

Chest CT scans from 43 patients with *SMARCA4*-dNSCLC revealed distinctive imaging patterns reflecting the disease's aggressive nature. Primary tumors frequently presented as large, mass-like soft tissue opacities with a predilection for the right upper lobe. These masses typically displayed ill-defined, spiculated margins with heterogeneous density and occasional internal calcifications. Many tumors exerted significant mass effect on surrounding structures, including bronchial compression, while adjacent lung parenchyma often showed increased density. Figure 2A illustrates these characteristic features, highlighting the tumor's invasive appearance.

Beyond the primary lesion, multifocal disease was common, manifesting as satellite nodules in other lobes. Peribronchial and peripheral ground-glass opacities frequently accompanied the primary mass, suggesting inflammatory changes or infectious processes. Notably, signs of underlying COPD, including increased lung lucency and thin-walled bullae, were prevalent, consistent with the high incidence of smoking history in this cohort. Figure 2B demonstrates both the mass effect on bronchial structures and concurrent COPD changes.

Table 2 Pathological and Immunohistochemical Results

Characteristic	n (%)
Histological Type	
Adenocarcinoma	28 (60%)
Squamous Cell Carcinoma	3 (6%)
Poorly Differentiated Carcinoma	6 (13%)
Undifferentiated Carcinoma	3 (6%)
Other	7 (15%)
Immunohistochemical Markers	
CK Positive	46 (98%)
CK7 Positive	30 (64%)
BRG-1 Complete Negative	43 (91%)
BRG-1 Partial Expression + *SMARCA4* Mutation	4 (9%)
TTF-1 Positive	17 (37%)
TTF-1 Negative	29 (63%)
Napsin A Positive	12 (36%)
Napsin A Negative	21 (64%)
P40 Positive	7 (16%)
P40 Negative	37 (84%)
PD-L1 <1%	17 (44%)
PD-L1 1–49%	20 (51%)
PD-L1 ≥50%	4 (10%)
Ki-67 >50%	25 (64%)

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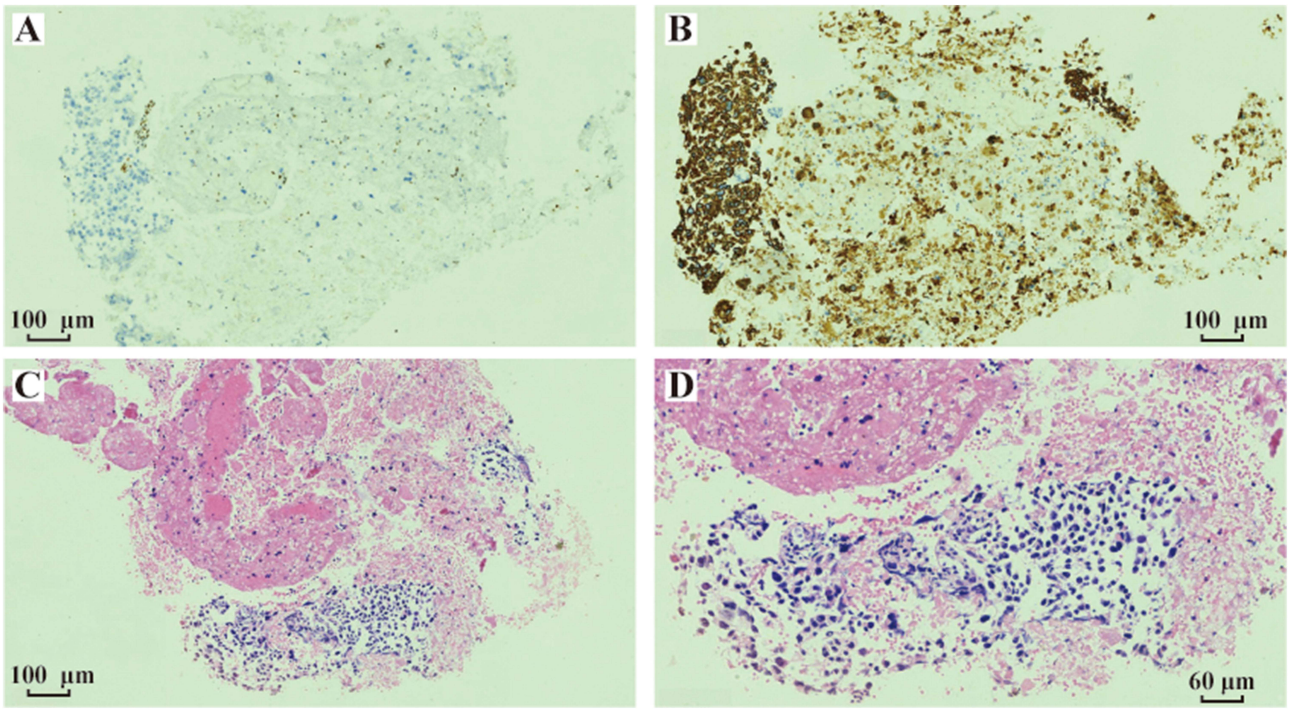

Figure 1 Representative Histopathological and Immunohistochemical Features of *SMARCA4*-dNSCLC. (**A**) Immunohistochemical staining demonstrates the loss of BRG1 nuclear expression in tumor cells (brown), with positive control in inflammatory cells (scale bar: 100 μm). (**B**) Immunohistochemical staining shows *CK* positivity in tumor cells (brown) (scale bar: 100 μm). (**C**) Hematoxylin and eosin (H&E) staining reveals coagulative necrosis and loosely cohesive, atypical tumor cells with high nuclear-cytoplasmic ratio, vesicular chromatin, and prominent nucleoli (scale bar: 100 μm). (**D**) Higher magnification H&E staining highlights the cellular atypia and necrosis in more detail (scale bar: 60 μm).

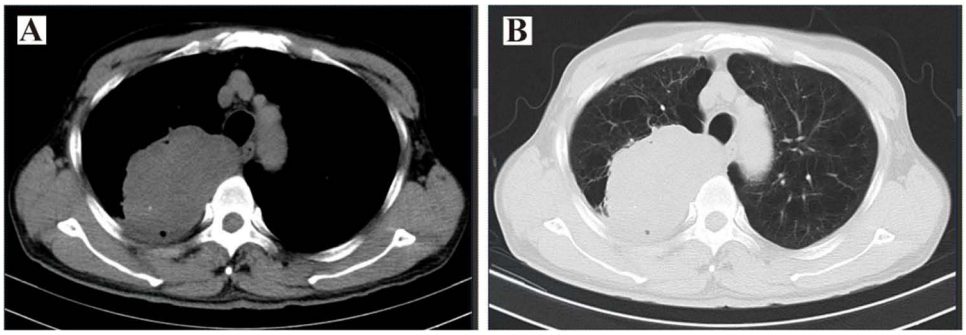

Figure 2 Representative chest CT images of *SMARCA4*-dNSCLC. (**A**) Axial chest CT (lung window) showing a large soft tissue mass in the right upper lobe with speculated margins and internal calcifications. (**B**) Axial chest CT (mediastinal window) showing displacement of the right upper lobe bronchus and patchy ground-glass opacities in both lungs.

Regional and distant spread was evident in many cases. Mediastinal lymphadenopathy appeared frequently, indicating lymphatic metastasis. Pleural involvement, characterized by small effusions, suggested either direct extension or inflammatory response. While not uniformly documented, adrenal gland evaluation remained important given this cancer's metastatic potential. Incidental findings included thyroid low-density lesions requiring further investigation and benign-appearing cystic lesions in the liver and kidneys. Collectively, these imaging features (large, invasive primary tumors with irregular margins, multifocal pulmonary disease, and regional spread) create a radiographic profile consistent with the known aggressive biological behavior of *SMARCA4*-dNSCLC. The key chest CT findings are detailed in Table 3.

Table 3 Key Chest CT Findings in *SMARCA4*-dNSCLC

Finding	Description	Potential Significance
Right upper lobe mass	Large soft tissue mass (eg, 9.6cm × 6.8cm), ill-defined, speculated, lobulated, heterogeneous density, possible calcifications	Aggressive primary tumor, local invasion
Bronchial displacement	Displacement/compression of right upper lobe bronchus	Mass effect of the tumor
Other pulmonary nodules	Nodules in other lobes (eg, right middle lobe)	Intrapulmonary spread, metastases
Peribronchial/peripheral opacities	Patchy ground-glass opacities	Inflammation, infection
Lung hyperlucency/bullae	Increased lung lucency, thin-walled bullae	COPD, emphysema
Mediastinal lymphadenopathy	Enlarged mediastinal lymph nodes	Lymph node metastasis
Pleural effusion	Small pleural effusion	Pleural involvement, metastasis, inflammation
Thyroid lesion	Low-density thyroid nodule	Requires further evaluation
Liver/kidney cysts	Cystic lesions in liver/kidney	Likely benign

Molecular Characteristics and Co-Mutations

To gain insights into the molecular underpinnings of *SMARCA4*-dNSCLC, we conducted next-generation sequencing (NGS) on a subset of 24 patients from the total cohort of 47. The selection criterion for these patients was based on the availability of adequate tissue samples and the clinical decision to perform molecular profiling to explore potential therapeutic targets. This molecular analysis aimed to uncover key molecular features and co-mutations that might influence disease progression and shape treatment strategies.

The NGS analysis revealed a notable absence of frequently targetable driver genes such as *EGFR* and *ALK* in the subset of *SMARCA4*-dNSCLC patients analyzed. A mere 4% of patients exhibited *EGFR* mutations, and no cases of *ALK* rearrangements were identified, suggesting a potential resistance to targeted therapies that are effective against these mutations. This information is visually represented in Figure 3A, which displays the mutation frequency of various molecular alterations identified by NGS, highlighting the rarity of *EGFR* and *ALK* mutations.

Furthermore, the analysis identified common co-mutations in genes known to be associated with lung cancer progression. Specific variants included *TP53* R273H (2 cases), *KRAS* G12C (1 case), *STK11* L148P (1 case), and *PIK3CA* E545K (1 case), co-occurring mutations were limited to 1 patient with *KRAS* G12C + *STK11* L148P. These co-mutations are recognized for enhancing tumor aggressiveness and could potentially influence the tumor's response to various treatments. The significance of these co-mutations is underscored by Figure 3B, that illustrates the proportion of patients with co-mutations in *TP53*, *KRAS*, and STK11, emphasizing their role in the molecular landscape of *SMARCA4*-dNSCLC.

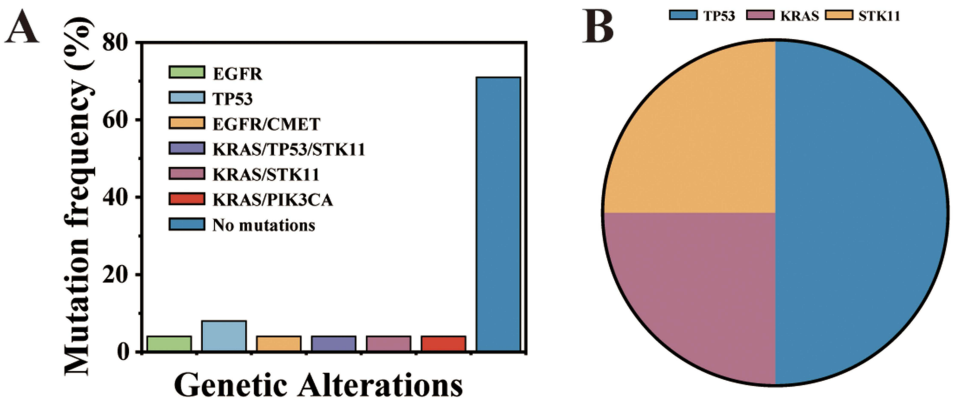

Figure 3 Molecular profiling data. (**A**) Bar chart showing the distribution of molecular alterations identified in the 24 patients. (**B**) Pie chart representing the proportion of patients with co-mutations in *TP53*, *KRAS*, and *STK11*.

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Notably, the co-occurrence of *TP53*, *KRAS*, and *STK11* mutations in this cohort may further enhance tumor aggressiveness by disrupting DNA damage repair and metabolic pathways, which is consistent with previous reports that *SMARCA4* deficiency synergizes with these mutations to promote malignant progression.[21,22] The rarity of *EGFR*/*ALK* mutations also explains the limited efficacy of conventional targeted therapies, highlighting the need for novel strategies targeting chromatin remodeling defects or co-mutated pathways.

In addition to these findings, the molecular analysis detected other alterations that could influence disease behavior. Mutations in *KEAP1* and *PIK3CA* were identified in a small subset of patients, indicating alternative pathways for tumor growth and resistance to therapy. These results suggest that while *SMARCA4*-dNSCLC may be less responsive to standard targeted therapies, the identified molecular alterations could guide the development of novel therapeutic strategies tailored to the specific molecular profile of the disease.

Treatment Patterns

Understanding the treatment patterns is crucial for evaluating the efficacy of various therapeutic approaches and identifying potential areas for improvement. We analyzed the treatment strategies employed for the 47 patients with *SMARCA4*-dNSCLC, focusing on the distribution across different disease stages and the types of treatments administered (Summarized in Table 4).

The treatment strategies varied significantly depending on the stage of the disease at diagnosis. For patients diagnosed with early-stage disease (Stages I and II), surgical resection was the primary treatment approach, often combined with adjuvant chemotherapy to reduce the risk of recurrence. Specifically, six patients with Stage I disease underwent surgery, three of whom also received chemotherapy. Among the six patients with Stage II disease, two underwent surgery alone, while the others received a combination of surgery and chemotherapy. For patients with more advanced disease (Stages III and IV), the treatment landscape was more complex. Thirteen patients with Stage III disease received a mix of treatments, including chemotherapy (with or without targeted therapy), immunotherapy (specific agents: sintilimab, atezolizumab, camrelizumab), and in some cases, a combination of these modalities. The selection of immune checkpoint inhibitors was based on clinical practice guidelines and patient performance status. Notably, one Stage III patient received Traditional Chinese Medicine as palliative supportive care, with the clinical rationale being poor performance status (ECOG PS score = 4) and refusal of chemotherapy/radiotherapy to alleviate symptoms.

A preliminary survival advantage was observed in the subgroup of patients receiving ICIs compared with chemotherapy-only patients in our cohort. Notably, recent studies have highlighted the intrinsic resistance of *SMARCA4*-deficient NSCLC to immune checkpoint inhibitors, which is closely associated with co-occurring mutations in *STK11* and *KEAP1*.[23,24] These mutations typically induce an "immune-cold" tumor microenvironment characterized by reduced

Table 4 Treatment Modalities by Stage

Treatment Modality	Stage I (n=6)	Stage II (n=6)	Stage III (n=13)	Stage IV (n=22)	Total (n=47)
Surgery	2	2	1	0	5
Chemotherapy	0	1	1	4	6
Surgery + Chemotherapy	3	2	0	0	5
Chemotherapy + Targeted Therapy	0	0	1	2	3
Chemotherapy + Immunotherapy	0	0	2	2	4
Surgery + Immunotherapy + Chemotherapy	1	1	1	1	4
Chemotherapy + Targeted Therapy + Immunotherapy	0	0	2	4	6
Immunotherapy + Chemotherapy + Radiotherapy	0	0	1	1	2
Surgery + Chemotherapy + Radiotherapy	0	0	0	1	1
Immunotherapy + Anti-angiogenesis	0	0	0	1	1
Traditional Chinese Medicine	0	0	1	0	1
No Treatment	0	0	3	6	9

infiltration of cytotoxic T lymphocytes and downregulated PD-L1 expression, thereby impairing the therapeutic efficacy of ICIs. In our cohort, the low frequency of *STK11*/*KEAP1* co-mutations may partially explain the observed preliminary survival benefit, though validation in larger cohorts is warranted.

The most challenging treatment decisions arose for the 22 patients with Stage IV disease, who were presented with distant metastases. The treatments for these patients were diverse, ranging from systemic chemotherapy and immunotherapy to targeted therapy for those with actionable mutations. Notably, nine patients did not receive any treatment due to personal reasons, economic constraints, or rapid disease progression, highlighting the need for more accessible and tolerable treatment options. Among the 9 untreated patients, 7 (77.8%) had ECOG PS score ≥3 (poor performance status) and 8 (88.9%) were at Stage IV with multiple distant metastases (higher disease burden), which may have contributed to the survival difference between treated and untreated groups.

A significant observation from this analysis was the heterogeneity in treatment approaches, even within the same disease stage. This variability underscores the complexity of managing *SMARCA4*-dNSCLC and the importance of personalized treatment plans. Additionally, the relatively high number of patients who did not receive treatment (9 out of 47) points to potential barriers in accessing care or the lack of suitable treatment options.

Survival Analysis and Prognostic Factors

The follow-up cutoff date of this study was July 28, 2024. The median follow-up time for the entire cohort (47 patients) was 10.5 months (interquartile range [IQR]: 6.8–14.2 months). Among them, the median follow-up time was 12.3 months (IQR: 8.5–15.1 months) in the treated group (n=38), 4.2 months (IQR: 2.8–5.6 months) in the untreated group (n=9), 13.1 months (IQR: 9.2–16.5 months) in the subgroup receiving immunotherapy (n=17), and 9.8 months (IQR: 6.1–13.3 months) in the subgroup not receiving immunotherapy (n=30). Survival analysis results showed significant differences in OS between the treated group (n=38) and untreated group (n=9). Kaplan-Meier survival curve analysis (Figure 4A) demonstrated that the median OS was not reached in the treated group, with a survival rate of 66% (25/38) and mortality rate of 34% (13/38), whereas the median OS in the untreated group was only 3 months (95% CI: 2.72–6.62 months). The 6-month and 12-month survival rates for the entire cohort were 62% (95% CI: 47–75%) and 32% (95% CI: 20–47%), respectively.

Overall, 26 patients (54.2%) survived and 21 patients (43.8%) died, including 2 patients who survived less than one month. The mean survival time for the entire cohort was 14.257 months (standard error 1.424, 95% CI: 11.466–17.047), with the median survival time not yet reached. The 6-month, 12-month, and 18-month survival rates were 62% (29/47), 32% (15/47), and 11% (5/47), respectively. Further subgroup analysis (Figure 4B) revealed that patients who received immunotherapy (n=17) had significantly higher overall survival rates compared to those who did not receive immunotherapy (n=30) ($p<0.05$), suggesting a potential survival benefit associated with immunotherapy in this cohort.

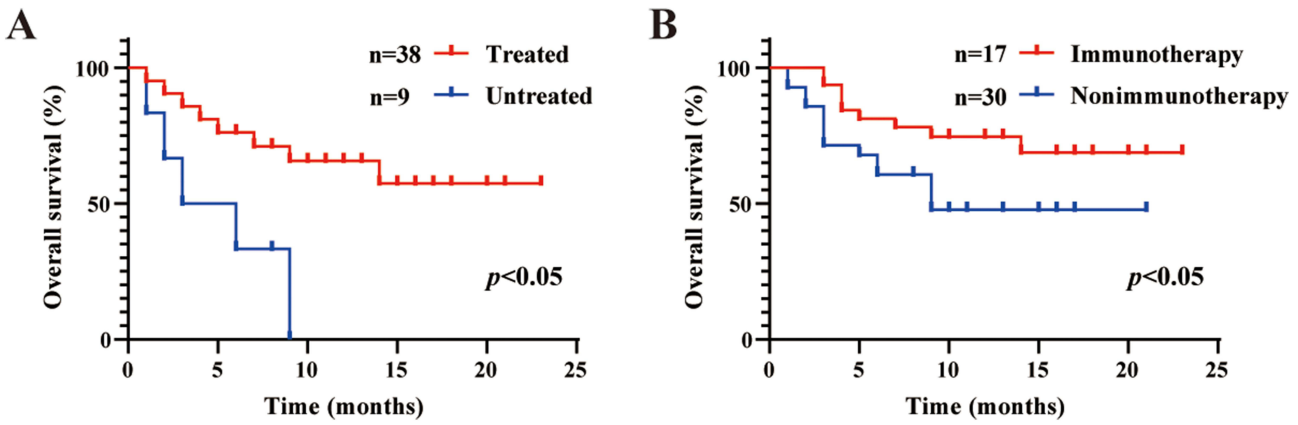

Figure 4 Overall survival analysis in patients with *SMARCA4*-dNSCLC. (**A**) Kaplan-Meier curves comparing overall survival between treated (n = 38) and untreated (n = 9) patients. (**B**) Kaplan-Meier curves comparing overall survival between patients who received immunotherapy (n = 17) and those who did not (n = 30). Statistical analysis was performed using the log-rank test, differences were statistically significant ($p < 0.05$).

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Table 5 Cox Regression Analysis of Factors Influencing Survival Time in *SMARCA4*-dNSCLC Patients

Factor	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years)	1.037 (0.988–1.090)	0.142		
Gender	2.740 (0.362–20.751)	0.329		
Smoking	2.740 (0.362–20.751)	0.471		
Alcohol consumption	0.511 (0.194–1.348)	0.175		
Family history	1.394 (0.184–10.564)	0.748		
Emphysema	0.502 (0.185–1.360)	0.175		
Tumor longest diameter (mm)	1.011 (0.995–1.026)	0.182		
Location	1.051 (0.817–1.351)	0.701		
Performance status (PS) score	3.206 (0.942–10.913)	0.062		
Ki-67	1.153 (0.16–8.329)	0.888		
PD-L1	1.081 (0.528~2.212)	0.831		
Lung cancer type	1.111 (0.907–1.359)	0.309		
TNM stage	5.147 (1.766–15.002)	0.003		
Distant metastasis	0.194 (0.067–0.566)	0.003	0.298 (0.117–0.756)	0.011
Treatment status (treated or untreated)	0.227 (0.090–0.572)	0.002	0.287 (0.108–0.765)	0.013

To investigate factors affecting survival time in *SMARCA4*-dNSCLC patients, Cox regression analysis was performed on 39 patients with complete data (Table 5). Univariate analysis showed that tumor TNM stage, treatment status, and distant metastasis were significantly associated with patient survival time ($p<0.05$). Multivariate regression analysis further confirmed that advanced TNM stage (HR=5.147, 95% CI: 1.766–15.002, p=0.003), lack of treatment (HR=0.227, 95% CI: 0.090–0.572, p=0.002), and distant metastasis (HR=0.194, 95% CI: 0.067–0.566, p=0.003) were independent risk factors for shortened survival time in patients with *SMARCA4*-dNSCLC.

These results suggest that the prognosis of patients with *SMARCA4*-dNSCLC is closely related to tumor stage, treatment status, and metastatic condition. For these patients, early diagnosis and active treatment are crucial, especially for those with advanced diseases, for whom comprehensive treatment strategies should be considered to improve prognosis.

Discussion

SMARCA4-dNSCLC represents a rare and aggressive subtype of non-small cell lung cancer (NSCLC) characterized by loss of BRG1 protein expression due to *SMARCA4* gene alterations. In line with previous studies, our cohort confirmed its strong association with male sex, heavy smoking history, and advanced age, with a median age of 66 years and 87% of patients being male. These findings support the notion that *SMARCA4*-deficient tumors are tightly linked to tobacco-related carcinogenesis.[15,25]

Consistent with its aggressive biological behavior, more than 60% of patients in this cohort were diagnosed at advanced TNM stages (Stage III–IV), and nearly half (47%) exhibited distant metastases at diagnosis. Common metastatic sites included the adrenal glands, pleura, and distant lymph nodes, reflecting the early and widespread dissemination pattern of this tumor type. Moreover, the frequent co-existence of underlying emphysema and chronic bronchitis, observed in over half of our cases, further underscores the etiological role of smoking and chronic lung damage in *SMARCA4*-deficient tumorigenesis.

Pathologically, adenocarcinoma was the predominant histologic subtype (60%), followed by poorly differentiated and undifferentiated carcinomas. Immunohistochemically, *SMARCA4*-deficient tumors displayed a characteristic profile with nearly universal BRG1 loss (91%), diffuse cytokeratin (CK) positivity, and a high *Ki-67* proliferative index, with over 50% of cases exhibiting Ki-67 >50%. Interestingly, only 37% of cases expressed *TTF-1*, reinforcing earlier reports that *TTF-1* negativity is a diagnostic clue for *SMARCA4* deficiency. PD-L1 expression was observed in more than half of

evaluable cases, with 56% showing ≥1% expression and 10% ≥50%, potentially indicating a role for immune checkpoint inhibition in selected patients.

Radiologically, *SMARCA4*-deficient tumors frequently manifested as large, ill-defined masses with central necrosis, bronchial truncation, and adjacent structure invasion, reflecting their aggressive and infiltrative growth pattern. Nearly 60% of patients exhibited lymph node metastases on imaging, and over 85% had patchy high-density lesions or nodules in other lung lobes. These imaging features, while not pathognomonic, may raise suspicion for *SMARCA4* deficiency in the appropriate clinical context.

Molecular profiling revealed a low prevalence of actionable driver mutations, with only one patient harboring an *EGFR* mutation. However, co-mutations involving *TP53*, *KRAS*, *STK11*, and *PIK3CA* were present in a minority of cases, aligning with previous genomic studies that have shown *SMARCA4*-dNSCLC to be enriched for tumor suppressor gene alterations rather than oncogenic drivers.[26,27] These findings emphasize the need for broader molecular screening to identify rare but potentially targetable alterations.

Despite the lack of standardized treatment strategies, our study suggests that therapeutic intervention, including surgery, chemotherapy, immunotherapy, and combination regimens, may confer survival benefits. The median OS in treated patients was not reached, while those without any treatment had a dismal median OS of only 3 months. Multivariate Cox analysis confirmed that advanced stage, distant metastasis, and absence of treatment were independent predictors of poor prognosis, underscoring the importance of early diagnosis and active management.

Several limitations of our study should be acknowledged. First, the single-center, retrospective design and relatively small sample size may limit the statistical power and generalizability of our findings. Second, the heterogeneity in treatment regimens and NGS testing platforms reflects real-world practice but may introduce confounding factors. In particular, the observed association between immunotherapy and survival is based on a small subgroup and requires validation in larger, prospective studies. Moreover, a potential limitation of this study is the confounding bias between treated and untreated groups, as untreated patients had poorer performance status and higher disease burden; future studies with propensity score matching may help reduce this bias.

In conclusion, *SMARCA4*-deficient NSCLC is a clinicopathologically and molecularly distinct entity associated with poor differentiation, advanced stage, high proliferative index, and limited treatment responsiveness. Consistent with our molecular profiling, this subtype exhibits a low prevalence of actionable driver mutations (eg, *EGFR*/*ALK*) but frequent co-mutations in tumor suppressor genes (*TP53*, *KRAS*, *STK11*), distinguishing it from common NSCLC subtypes. Notably, subgroup analysis suggests a potential survival benefit of immunotherapy in selected patients, particularly those with non-negligible *PD-L1* expression or absence of *STK11*/*KEAP1* co-mutations. Our findings also highlight the need for strengthened routine BRG1 immunohistochemical (IHC) screening in high-risk populations (eg, older male smokers with advanced NSCLC) to improve early recognition of this rare subtype. Overall, our study underscores the importance of heightened clinical awareness, early diagnostic workup (including IHC for *BRG1*), and consideration of individualized therapeutic approaches. Further multicenter prospective studies and molecularly guided trials are warranted to develop effective treatment strategies and improve outcomes in this challenging patient population.

Further multicenter prospective studies and molecularly guided trials are warranted to develop effective treatment strategies and improve outcomes in this challenging patient population. Building on our findings, future translational research should prioritize several key directions. These include evaluating novel therapeutic agents that target epigenetic vulnerabilities or specific co-mutations such as *KRAS* or *STK11* in *SMARCA4*-dNSCLC, identifying predictive biomarkers beyond PD-L1, particularly tumor mutational burden and features of the immune microenvironment, to optimize patient selection for immunotherapy, and developing non-invasive diagnostic or monitoring tools that exploit the distinctive imaging or molecular signatures characteristic of this aggressive subtype.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data will be shared in a de-identified format to protect patient privacy. Requests for data access should be directed to

Qingming Shi (email: shqm0324@163.com). Data requestors will need to sign a data access agreement to ensure the confidentiality and appropriate use of the data.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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